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The Immunometabolic Network of Diabetes Mellitus: A Review of its Mechanisms, Complications and Therapeutic Implications

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Abstract

Diabetes mellitus is defined clinically by dysglycaemia but the initiation, progression and complications of diabetes are the result of reciprocal interactions between nutrient sensing, cellular stress and immune regulation. This narrative review summarizes the evidence for immunometabolic mechanisms linking insulin resistance, β-cell dysfunction and multi-organ injury. In type 1 diabetes, β-cell loss is largely driven by adaptive autoimmunity . Metabolic stress plays a role in modulating disease tempo, but this should not be confused with the initiating mechanism. In type 2 diabetes, reinforcing loops of adipose dysfunction, ectopic lipid deposition, altered insulin signaling, endoplasmic-reticulum stress, mitochondrial impairment and innate immune activation progressively erode insulin sensitivity and β-cell reserve. Activation of the NLRP3 inflammasome and interleukin-1 signaling are paradigms of molecular convergence of metabolic danger signals and inflammation. Persistent oxidative, epigenetic and inflammatory changes also contribute to metabolic memory. This helps explain why earlier glycemic exposure influences later vascular risk. Common processes—endothelial dysfunction, redox imbalance, mitochondrial injury and fibrotic signalling—are differentially expressed in the heart, kidney, retina, peripheral nerves and periodontal tissues. Since glucose, blood pressure, lipids, weight and cardiorenal risk are still actionable treatment anchors, clinical translation requires some restraint. In addition, most inflammatory and multi-omics biomarkers are still investigational. Thus, immunometabolic therapy is not a replacements but it should be an adjunct to established risk-factor management. Mechanism-informed intervention shows both promise and limitations, as demonstrated by stage-specific teplizumab in type 1 diabetes, incretin-based therapies, sodium-glucose cotransporter 2 inhibitors, and select anti-inflammatory trials.

INTRODUCTION

Glucose disregulation disorder (Diabetes mellitus) is a group of chronic diseases characterized by persistent hyperglycaemia but differing in etiology, course and treatment [1–5]. Type 1 diabetes is characterized by immune-mediated destruction of pancreatic β-cells and progressive loss of endogenous insulin secretion [6,7,29,30]. Type 2 diabetes is the most prevalent form of diabetes and occurs when insulin resistance in liver, skeletal muscle and adipose tissue cannot be compensated sufficiently by β-cell compensation [3–5,22–28]. Gestational diabetes, monogenic diabetes and secondary diabetes add to the biological diversity. Thus, a useful framework should explain shared pathways without collapsing these conditions into a single inflammatory composition. Epidemiology implications are especially relevant in Africa, where demographic growth, aging, urbanization and changing food environments overlap with constraints on screening and long-term care. WHO estimated that in its African Region, over 24 million adults aged 20–79 years will be living with diabetes in 2025, with the total projected to

reach 60 million by 2050, and nearly half remain undiagnosed [53]. Late diagnosis of diabetes do increase the risk of vascular or neurological complications at presentation. In addition, limited access to testing, medicines and co-ordinated primary care magnifies the preventable harm. Nigeria demonstrates both the magnitude and the uncertainty of the burden. A meta-analysis of 60 studies in Nigeria with a total of 124,876 participants, estimated the pooled prevalence of type 2 diabetes in 2024 to be 7.0% (95% confidence interval 5-9%) [51]. Estimates varied by setting and geopolitical region, due to differences in age, adiposity, urbanization, sampling and diagnostic criteria. Thus, the pooled percentage cannot be used to calculate the number of cases in the total population to get the national case number. But the evidence indicates a high caseload together with hypertension, obesity, family history and low awareness, making earlier detection and context-appropriate risk reduction priorities for Nigerian healthcare.

Coverage and prevalence of treatment are still uneven across the globe. A study of 1,108 population-representative studies including 141 million adults found dramatic increases in diabetes prevalence from 1990 to 2022 and large treatment gaps, particularly in low and middle-income settings [52]. Energy imbalance and insulin resistance remain central but do not fully explain the persistence of dysfunction, the variable rate of decline of β-cell reserve or the clustering of complications in individuals. Genetic susceptibility, ectopic lipid, nutrient sensing, organelle stress and immune activation interact across tissues, with variable contributions by diabetes type, disease stage, ancestry and treatment risk.

Immunometabolism offers a conceptual framework to study this bidirectional relationship between cellular metabolism and immune function. Nutrient excess, hypoxia, lipotoxicity and organelle stress may re-programme innate and adaptive immune cells. Cytokines, inflammasomes and stress kinases (**Table 1**) may then alter insulin signaling, substrate handling, β-cell function and tissue repair [8,23,33,34]. For type 1 diabetes, these pathways are active in the setting of an antigen-specific autoimmune process. In type 2 diabetes, sterile low-grade inflammation often exacerbates metabolic stress and tissue dysfunction. This is important because a circulating inflammatory marker may indicate risk without revealing the causal pathway in the organ affected or predicting benefit from immune-directed therapy.

This narrative review discusses the immunometabolic network between insulin resistance, β-cell failure and chronic complications. It discusses adipose remodeling, ectopic lipid, organelle stress, NLRP3–interleukin-1 signaling, oxidative injury and metabolic memory and reviews their expression in cardiovascular, renal, retinal, neural and periodontal disease. The disconnect between molecular associations and actionable evidence is highlighted. In light of the increasing burden in Nigeria and Africa, the translational question is which pathway is causal, measurable and modifiable in a defined patient at a given disease stage.

Divergent Initiating Mechanisms, Convergent Downstream Stress

Diabetes Type 1

Transmissible predisposition, especially in HLA loci, interacts with poorly defined environmental factors to trigger the loss of immune tolerance to islet antigens [6,7,29,30]. Autoantibodies define risk and stage disease, and autoreactive T cells mediate much of the β-cell injury. C-peptide is a clinically useful estimate of residual insulin secretion [31]. Metabolic stress and innate inflammation may promote injury but autoimmunity is the determine instrument.

Diabetes type 2

Diabetes type 2, insulin resistance develops in skeletal muscle, liver and adipose tissue, with progressive failure of β-cells [22,23,32,33]. Diacylglycerols, ceramides and related lipid intermediates activate kinases which interfere with insulin signaling. Initially hyperinsulinaemia is compensatory but as β-cell identity, secretory capacity and survival decline, remuneration collapses.

Glucose disregulation disorder can be classified into mechanistically distinct monogenic forms, and identifying pathogenic variants can directly change treatment. As an example, many patients with activating KCNJ11-related neonatal diabetes can transition from insulin to sulfonylureas [9,10]. This provides a useful benchmark for precision immunometabolism: mechanistic classification should lead to a reproducible clinical action, not merely a more complex mark.

Table 1. Immunometabolic distinctions between major diabetes types.

Feature	Type 1 diabetes	Type 2 diabetes
Defining lesion	Immune-mediated β-cell destruction	Insulin resistance with progressive β-cell dysfunction
Key susceptibility	HLA and immune-regulatory genetics	Polygenic metabolic susceptibility plus environment
Immune pattern	Antigen-specific adaptive autoimmunity with innate contributions	Sterile, low-grade inflammation secondary to metabolic stress
Insulin state	Absolute or near-absolute deficiency	Variable resistance and relative deficiency
Actionable markers	Islet autoantibodies and C-peptide	Clinical phenotype, C-peptide in selected cases, cardiorenal risk
Core treatment	Insulin; stage-specific immune therapy in eligible presymptomatic disease	Lifestyle and weight management; glucose- and organ-protective pharmacotherapy

Nodes of The Immunometabolic Network

Adipose tissue inflammation

Adipocytic cell hypertrophy increases hypoxia, lipolysis, extracellular-matrix stress and chemokine release Recruitment of macrophages and altered T-cell populations drive adipose signaling into a pro-inflammatory state. TNF, IL-6 and related mediators (**Table 2**) activate JNK and IKK–NF-κB pathways that down-regulate insulin-receptor substrate signaling [8,33,34]. Human adipose biology is more heterogeneous than simplified M1/M2 models suggest, immune phenotype is continuous and storage reliant.

Insulin signaling and ectopic lipids

Signaling Insulin in the canonical pathway is mediated through the insulin receptor, IRS proteins, PI3K and Akt. Activation of protein kinase C isoforms and stress kinases by lipids derails this cascade, resulting in reduced muscle glucose uptake and failure to suppress hepatic glucose production [22,23,33]. Branched-chain amino-acid and lipid signatures are associated with insulin resistance but are not yet standalone treatment selectors [11,12,35,36]. The composition of gut microbes and microbial metabolites may influence barrier function and metabolic inflammation, but medication, diet, geography and laboratory workflow are major confounders. Microbial signatures associated with metformin exemplify why cross-sectional microbiome associations cannot be assumed to define a causal endotype diabetes [13].

β-cell stress, mitochondria and endoplasmic reticulum

β-cells need to couple nutrient oxidation to ATP production and insulin secretion, with the maintenance of high rates of proinsulin synthesis. Chronic demand can overburden protein folding capacity, activate the unfolded-protein response and disturb calcium homeostasis. Mitochondrial dysfunction impairs stimulus-secretion coupling and excessive reactive oxygen species damage proteins, lipids and DNA. These pathways do not form a single, linear sequence, but interact with one another (**Fig. 1**).

NLRP3 & innate immune signalling

The NLRP3 inflammasome is a platform that recognizes danger signals from ion flux, mitochondrial injury and cellular debris to activate caspase-1 and mature IL-1β and IL-18. NLRP3 is strongly implicated in metabolic inflammation in experimental models, but human therapeutic data are more sparse. Canakinumab was associated with reduction in recurrent cardiovascular events in an inflammation-selected population but also with increased fatal infection and did not establish broad anti-inflammatory for diabetes treatment [20,21].

Table 2. Principal immunometabolic pathways and evidentiary interpretation.

Pathway	Representative trigger	Biological consequence	Clinical status
JNK/IKK–NF-κB	Cytokines, fatty acids, organelle stress	Inhibitory insulin-signalling changes and inflammatory transcription	Mechanistically strong; not a routine biomarker
NLRP3–IL-1	Mitochondrial danger signals and cellular stress	IL-1β/IL-18 maturation and pyroptotic signalling	Therapeutic target under investigation
ER stress	Protein-folding demand and lipotoxicity	Adaptive UPR or apoptosis when unresolved	Predominantly experimental
Oxidative stress	Mitochondrial overload and hyperglycaemia	Macromolecular damage and redox signalling	Shared mechanism; antioxidant trials not uniformly beneficial
Fibrotic signalling	Chronic injury, TGF-β and inflammation	Extracellular-matrix deposition and organ remodelling	Organ-specific treatment remains central

Metabolic memory

Inadequate glycemic control during early periods may influence later risk for complications even after improvement later. This legacy effect is supported by long-term follow-up of intensive-control trials. Possible mechanisms include persistent epigenetic marks, advanced glycation, mitochondrial ROS generation and persistent inflammatory programming. Metabolic memory does not imply that later control is futile but rather highlights the need for safe early control and sustained multifactorial danger decline [2,14–16,43–46].

Common mechanisms in organ complications

Ordinary system exposures and organ-specific susceptibility result in diabetes complications. Endothelial dysfunction, altered nitric-oxide signaling, oxidative injury, inflammation and fibrosis contribute across tissues but the cellular context and differ in clinical endpoints.

Heart Disease

Atherosclerotic risk in diabetes is a composite of dyslipidemia, hypertension, glycemic exposure, thrombosis and vascular inflammation. Cardiovascular-outcome trials show that GLP-1 receptor agonists and SGLT2 inhibitors reduce events by mechanisms that are not only explained by the change in HbA1c [14–18,43,44,50]. Treatment should be driven by established cardiovascular risk and indication, not by an unvalidated inflammatory signature (**Fig. 2**).

Diabetic nephropathy

The features of diabetic kidney disease are implications including glomerular hyperfiltration, injury to podocytes and endothelium, tubular metabolic stress, inflammation and TGF-β-mediated fibrosis. Clinical trials of SGLT2 inhibitors revealed significant renal protection in high-risk diabetic populations [45,46]. These clinical effects support mechanism-informed therapy but emphasize that organ phenotype and estimated risk are the practical option instruments.

Neuropathy and Diabetic retinopathy

Retinopathy is connected with neurovascular unit dysfunction, capillary leakage, ischemia and neovascularization. Neuropathy is made up of axonal metabolic injury, mitochondrial dysfunction, microvascular insufficiency and neuroinflammation. Good glycemic control remains preventive, but the individual trajectories are altered by duration, prior exposure and other danger causes.

Gum disease

Diabetes accelerates periodontal inflammation via altered neutrophil function, advanced glycation, impaired repair, and dysregulated host-microbial interactions. Although treatment of periodontitis may add to systemic inflammatory burden, it should not be offered as a substitute for diabetes management.

Table 3. Shared mechanisms expressed across major diabetes complications.

Organ system	Dominant manifestations	Contributing immunometabolic processes
Cardiovascular	Atherosclerosis, myocardial dysfunction and heart failure	Endothelial dysfunction, lipid stress, inflammation and fibrosis
Kidney	Albuminuria and progressive loss of filtration	Haemodynamic stress, tubular metabolism, inflammation and fibrosis
Retina	Leakage, ischaemia and neovascularisation	Neurovascular dysfunction, oxidative stress and inflammation
Peripheral nerves	Pain, sensory loss and autonomic dysfunction	Axonal metabolic injury, mitochondrial dysfunction and neuroinflammation
Periodontium	Inflammation, attachment loss and impaired healing	Dysregulated host–microbial response and advanced glycation

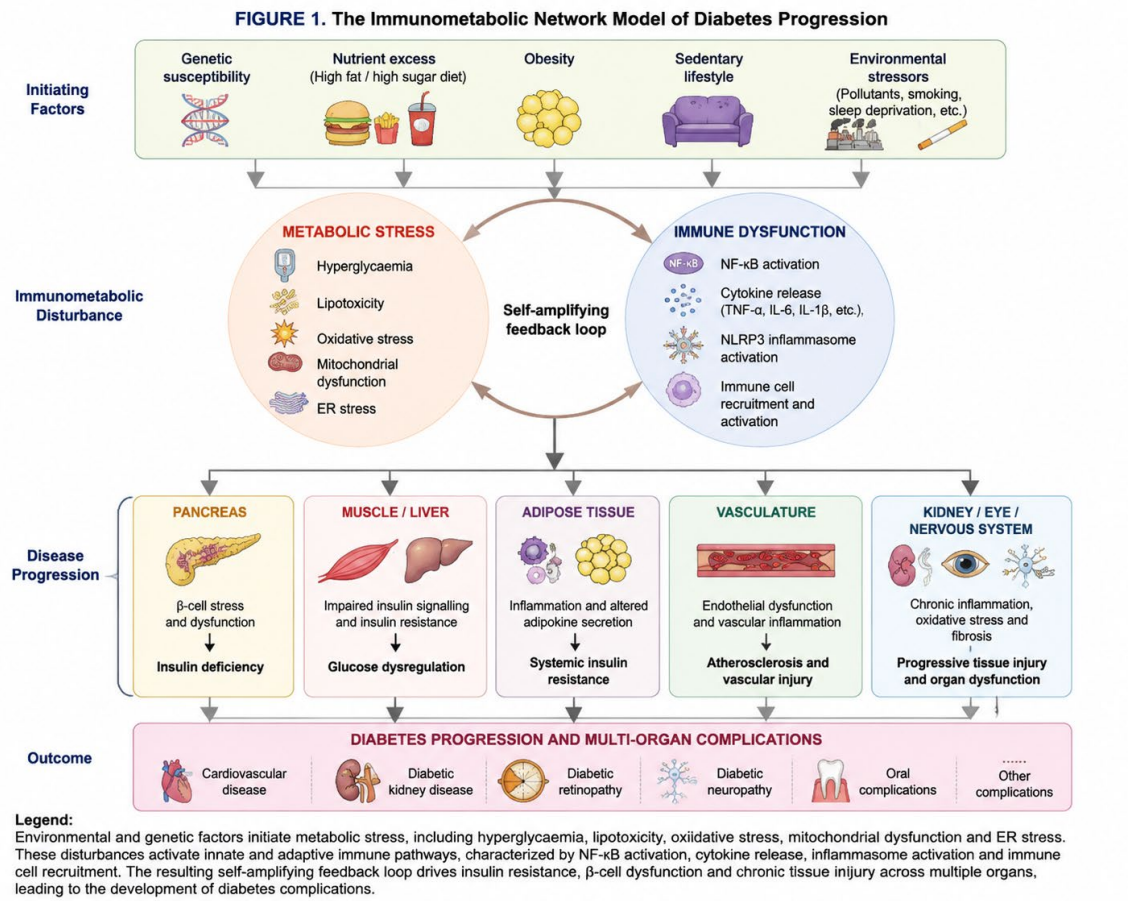

Fig. 1. Conceptual immunometabolic network of diabetes progression. Genetic and environmental inputs interact with metabolic stress and immune dysfunction. The relative importance and causal order differ between type 1 and type 2 diabetes; arrows indicate plausible bidirectional relationships rather than quantified effects.

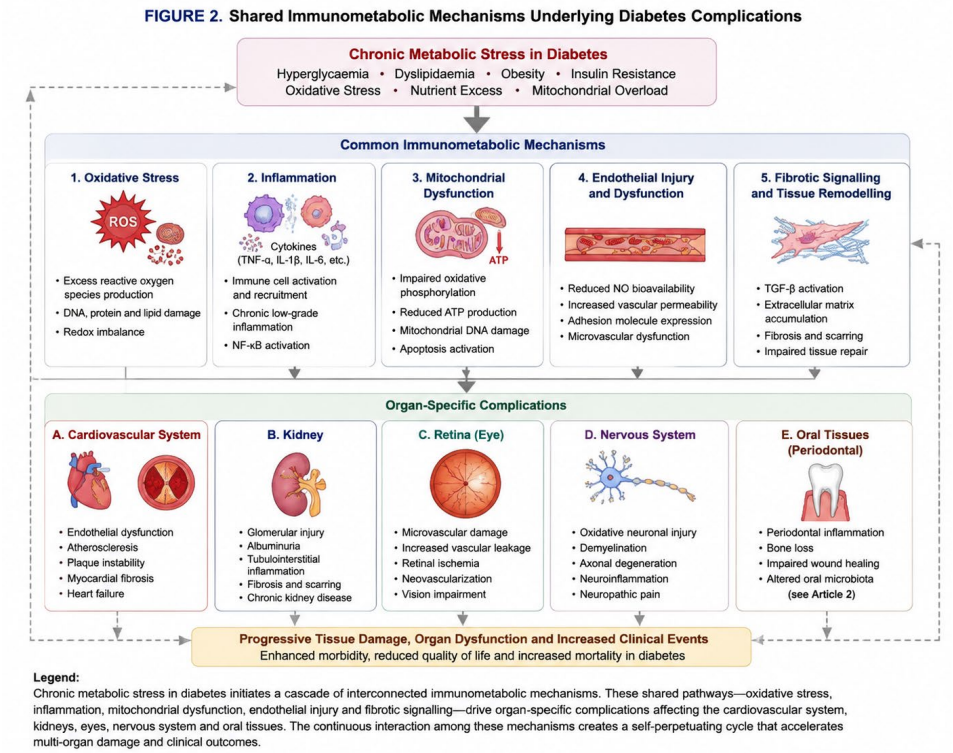

Fig. 2. Shared immunometabolic mechanisms underlying diabetes complications. Oxidative stress, inflammation, mitochondrial dysfunction, endothelial injury and fibrosis interact across organs. The diagram is conceptual and does not imply identical pathway strength in every complication.

Clinical implications

Rationalistic perception has clinical utility only to the extent that it improves a decision. The cornerstones remain early control of glucose, blood pressure and lipids. Metabolic load is reduced by weight loss and incretin-based therapy; GLP-1 receptor agonists and tirzepatide have large mean glucose and weight effects [14–18,47–50]. SGLT2 inhibitors have cardiorenal protection [43-46]. An example of stage-specific immune intervention in type 1 diabetes is teplizumab [19]. Such successes do not warrant broad immune suppression or indiscriminate biomarker panels. In the Diabetes Prevention Program, lifestyle intervention reduced progression to type 2 diabetes among high-risk adults [41]. However, in Look AHEAD, an intensive lifestyle intervention in people with established type 2 diabetes did not reduce cardiovascular events despite sustained improvements in weight and fitness [42]. The difference accounts for why we need to separate intermediate metabolic improvement from hard clinical outcomes. A framework for precision should be based on the clinical question, employ validated biomarkers where they change diagnosis or treatment, and evaluate complex models against simple clinical predictors [1,24–28,37–40]. Real heterogeneity is revealed by multi-ancestry genetic studies and physiological subphenotyping [24–27], but implementation requires external validation, calibration, practicability and fairness.

Limitations and research priorities

Several studies that warrant future works should link tissue-resolved immunology to longitudinal phenotypes, prospectively test treatment-by-biomarker interactions, and be able to distinguish causal mediators from correlates. It is also known that genetic scores and molecular classifiers may not translate well across ancestries [26–28,37–40] and so genetic diversity is required. Transparent analysis, standardized sampling, and clinically meaningful endpoints should replace larger untargeted panels. The way this narrative review is constructed is that we did not use a registered systematic-review protocol and does not provide pooled effect estimates. What we aim is for the combination of mechanisms. Since there is some evidence from human trials, observational cohorts and experimental models, claims are therefore qualified according to the strength and directness of the evidence.

CONCLUSIONS

Diabetes needs to be viewed as a group of disorders in which metabolic and immune processes interact at many levels. Generally, Type 1 diabetes is characterized by autoimmune destruction of β-cells, whereas in type 2 diabetes, sterile inflammation is a key amplifier, and is primarily characterized by insulin resistance and β-cell failure. Adipose remodeling, ectopic lipid, organelle stress, NLRP3 signaling and oxidative injury represent interrelated nodes that contribute further to complications. The immunometabolic paradigm is most useful where it illuminates mechanisms of disease, without masking aetiological differences or over-stating experimental targets. Translation priorities are early multifactorial risk reduction, therapies with proven organ benefit, and biomarkers that optimize clinical decisions in a measurable way.

AUTHOR CONTRIBUTIONS

F.Y.M.: Conceptualization, Methodology, Investigation, Project administration, Writing – original draft. I.A.A.: Investigation, Methodology, Data curation, Formal analysis, Writing – original draft. J.D.U.: Supervision, Conceptualization, Project administration, Writing – review & editing. S.I.: Investigation, Formal analysis, Validation, Writing – review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

All data supporting the findings of this study are included within the manuscript.

SUPPLEMENTARY DATA

Not applicable.

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